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Algorithm To Determine Cost Savings of Targeting Antimicrobial Therapy Based on Results of Rapid Diagnostic Testing

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A rapid diagnosis of pneumococcal pneumonia may allow the earlier use of narrow-spectrum antimicrobial therapy. It is unknown, however, whether rapid diagnostic testing of patients hospitalized with community-acquired pneumonia (CAP) admitted to hospital lowers costs. Therefore, an algorithm to calculate the costs associated with the diagnosis and treatment of CAP was formulated. Subsequently, the algorithm was applied to clinical data for 122 consecutively admitted patients with CAP whose sputum samples were Gram stained and whose urine was tested for *Streptococcus pneumoniae* antigen. The costs of initial antimicrobial therapy, personnel, and materials were measured. Compared to the most expensive empirical regimen, rapid diagnostic testing would result in cost savings per patient (PP) of €3.51 for Gram staining and €8.11 for urinary pneumococcal antigen testing (€1 is equal to US$1.13, from 2000 to 2002). Compared to the cheapest regimen, Gram staining would increase the cost by €2.25 PP, and urinary antigen testing would increase the cost by €24.26 PP. In our setting, the use of rapid diagnostic testing would not lower costs. Cost savings depend, however, on the differences in the prices of the different antibiotics chosen and the proportion of evaluable and positive samples.

In addition to therapeutic efficacy, rising costs have become a major concern in the treatment of patients with serious infections. An important factor associated with the high costs of treatment for these patients is the unnecessary use of broad-spectrum antibiotics. Therefore, apart from microbiological and therapeutic considerations, from an economical perspective, strategies to decrease the unnecessary use of these agents are needed. In an attempt to cover all suspected pathogens, initial antibiotic therapy is often broad spectrum. The results of microbiological investigations can help target the antimicrobial therapy to the isolated pathogens, an approach known as "streamlining" (13). However, the results of diagnostic procedures such as microbiological cultures or serological tests have delays of days to weeks and are therefore not suitable as guides to therapy in an early stage of the disease. Other diagnostic procedures, however, yield almost instantaneous results and could potentially be useful in guiding initial antimicrobial therapy.

In an analysis described here, we evaluated the potential cost savings associated with the use of rapid diagnostic tests to guide initial antimicrobial therapy in patients hospitalized with community-acquired pneumonia (CAP). As the causative microorganism cannot be predicted from clinical, laboratory, or radiological findings (8, 17, 28), initial antimicrobial therapy is mostly empirical and covers different potential pathogens. Among the different pathogens, *Streptococcus pneumoniae* is the most prevalent microorganism causing disease and is found in up to 40% of episodes of CAP (14, 15, 21). Especially in areas with low resistance rates, *S. pneumoniae* infections can be adequately treated with narrow-spectrum antibiotics, such as penicillin G or amoxicillin, instead of more broad-spectrum agents, such as ceftriaxone (with or without a macrolide) or levofloxacin (25). The diagnostic procedures that can be used in the diagnostic workup of CAP and that provide results within minutes include Gram staining of sputum and antigen testing for pneumococci in urine. The advantages of Gram staining of sputum include its wide availability and low cost. However, adequate sputum samples cannot always be obtained, either because there is no sputum production or because samples are not adequate for evaluation. Furthermore, the sensitivity and specificity of the method are unknown, some bacteria are difficult to identify or cannot be identified, and a uniform definition of a positive staining result does not exist (20, 23). For these reasons, the use of Gram staining of sputum in the diagnosis and management of CAP is controversial: its use is recommended by the Infectious Diseases Society of America but not by the American Thoracic Society (1, 2). Another way to rapidly diagnose pneumococcal pneumonia is urinary antigen testing. An immunochromatographic test, the NOW *Streptococcus pneumoniae* urinary antigen test (Binax, Inc., Portland, Maine), detects the C polysaccharide wall antigen common to all *S. pneumoniae* strains (22), with results being available within 15 min. Preliminary results suggest that this method has a specificity of 90 to 100% and a sensitivity of 74% (19). Another report showed a lower specificity: test results could also be positive for patients who are nasopharyngeal carriers of pneumococci (5).

The rapid diagnosis of pneumococcal pneumonia may result

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in the use of cheaper empirical antibiotics. However, it is unknown whether the potential cost savings outweigh the costs for personnel and materials. Therefore, we developed a simple algorithm to assess the potential costs and savings associated with the use of rapid diagnostic testing for pneumococcal pneumonia using Gram staining of sputum or a urinary pneumococcal antigen test and evaluated the cost savings for 122 consecutively admitted patients with CAP.

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MATERIALS AND METHODS

Patients and setting. The study was approved by the local ethics committee, and all patients provided informed consent to participate in the study. The University Medical Centre Utrecht is a 1,042-bed tertiary-care hospital. The Department of Medicine consists of two general internal medicine wards and one ward for acute medicine and infectious diseases. Together they accounted for 3,036 admissions in 2001. All patients with severe CAP of Fine class IV or V, as defined by Fine et al. (9), or patients who fulfilled the criteria of the American Thoracic Society (1) for severe CAP and hospitalized on internal medicine wards in the University Medical Centre Utrecht between November 2000 and November 2002 were included in the study. Patients who needed mechanical ventilation in an intensive care unit were not included. Initial therapy, age, and the severity of pneumonia, as defined by Fine et al. (9), were documented. CAP was defined as a new or progressive infiltrate on chest X ray and two or more of the following: cough, production of purulent sputum, rectal temperature above 38°C or below 36°C, auscultatory findings consistent with pneumonia, leukocytosis (>10,000/mm^3), and C-reactive protein levels more than three times the upper limit of normal. Patients with cystic fibrosis, neutropenic patients ($<0.5 \times 10^9$ neutrophils/liter), and patients with another infection requiring treatment were excluded. All patients were encouraged to provide a sputum sample and a urine sample; however, in the analysis we only used samples provided within 24 h of hospitalization.

Microbiological assessment. Sputum samples were evaluated in the microbiological laboratory and Gram stained by standard techniques. Sputum samples were considered evaluable if no more than 10 squamous epithelial cells and no more than 20 neutrophils per low-power field were visible and were considered positive for pneumococci when >10 gram-positive cocci per low-power field were present as the predominant organism. We used the NOW *Streptococcus pneumoniae* urinary antigen test, provided by Binax, Inc., to identify pneumococcal urinary antigen. Samples were evaluated serologically for *Chlamydia pneumoniae*, *Chlamydia psittaci*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*. The blood and sputum samples were cultured, and the cultures were evaluated by standard procedures. In addition, we used a urinary antigen test (NOW; Binax, Inc.) to identify *L. pneumophila*.

Cost assessment. The costs of antimicrobial agents were based on the actual costs of the antibiotics paid by the Department of Clinical Pharmacy of the University Medical Centre Utrecht. We calculated the potential cost reduction that could be achieved if therapy was streamlined on the basis of the results of rapid diagnostic tests before culture results became available. Therefore, only the costs of antimicrobials for the first 3 days of therapy were calculated. The durations of preparation and handling of the medications were measured twice for all relevant antibiotics. The average costs per antibiotic and per combination of antibiotics were calculated for 3 days; these included the costs for personnel (nurses wages for the time used for antibiotic preparation and administration) and the materials used (needles, syringes, antibiotics, intravenous solutions, etc.), as described previously (11).

Diagnostic costs (i.e., costs for preparation and examination of Gram stains and performance of the urinary antigen test) were based on the hospital's tariff system, which includes the wages for personnel and the costs for materials. We formulated an algorithm to evaluate the potential cost reduction.

Algorithm to analyze cost reduction. In the algorithm for cost reduction, it was assumed that antimicrobial therapy would be streamlined on the basis of a positive urinary pneumococcal antigen test result or a positive Gram staining result. Only samples obtained on the first day of hospitalization and of sufficient quality for microbiological analysis were used. Patients without a positive test result because sampling was not performed at all, because sampling was not performed within 24 h hospitalization, or because test results were negative received broad-spectrum therapy. The difference in the cost of targeted narrow-spectrum therapy based on positive diagnostic test results and the cost of empirical and broad-spectrum therapy was defined as a cost reduction, which could be expressed as the cost for empirical therapy − (cost for targeted therapy in patients with positive test results + cost for empirical therapy in patients with negative test results + cost of diagnostic procedures). This can be expressed by the following formula:

$$\text{Cost reduction} = N_p \cdot C_{\text{Emp}} - \{P_{\text{Ev}} \cdot P_{\text{Pos}} \cdot C_{\text{Targ}} + [N_p - (P_{\text{Ev}} \cdot P_{\text{Pos}})] \cdot C_{\text{Emp}} + C_{\text{Dx}} \cdot N_{\text{Tests}}\}$$

where N_p is the number of patients, C_{Emp} is the cost of empirical therapy, P_{Ev} is the percentage of adequate samples, P_{Pos} is the percentage of positive adequate samples, C_{Targ} is the cost of targeted therapy, C_{Dx} is the cost of the diagnostic test, and N_{tests} is the number of tests that can be performed.

Resolution of this equation results in

$$\text{Cost reduction} = (N_p \cdot P_{\text{Ev}} \cdot P_{\text{Pos}} \cdot \Delta P) - (N_{\text{tests}} \cdot C_{\text{Dx}}) \quad (1)$$

where ΔP is the difference in price between empirical therapy and targeted therapy.

Sensitivity analysis. A sensitivity analysis was performed by calculating the cost outcomes when P_{Ev}, P_{Pos}, and ΔP varied.

RESULTS

Patients. One hundred twenty-two consecutive patients (84 of whom were males) admitted with CAP were evaluated (N_p = 122). The mean age of the population was 67.20 years (standard deviation, 14.50 years; range, 28 to 96 years), and the mean Fine score was 110.79 (standard deviation, 28.17; range, 45 to 195). Sixty-seven (54.9%) patients fell in Fine pneumonia severity index risk class IV, 27 (22.1%) patients fell in Fine risk class V, and 26 patients (21.7%) fulfilled the criteria of the American Thoracic Society for severe CAP (1, 9). Initial therapy consisted of amoxicillin-clavulanic acid in 56 (46%) patients, amoxicillin-clavulanic acid in combination with a macrolide in 12 (10%) patients, ceftriaxone in 43 (35%) patients, and ceftriaxone in combination with a macrolide in 5 patients. One patient was switched from amoxicillin-clavulanic acid to erythromycin plus rifampin as soon as a urinary antigen test indicated *L. pneumophila* infection, one patient received trimethoprim-sulfamethoxazole, and one patient was treated with ciprofloxacin.

Twenty-eight (23%) patients had received prior antibiotic treatment before hospital admission. Ultimately, a causative agent for CAP was identified in 54 of 122 (44%) patients (Table 1). In another 12 (10%) patients a positive urinary antigen test was the only indicator of *S. pneumoniae* infection. Sputum samples from 52 patients (43%; N_{tests} = 52) were Gram stained during the first day of hospitalization. Of these 52 samples that were Gram stained, 23 (19% of all patients) were evaluable (P_{Ev} = 0.19), and gram-positive cocci could be identified in 10 samples. However, gram-positive cocci were considered the predominant microorganism in only 7 of these 52 samples (P_{Pos} = 0.13). Another predominant microorganism was identified in one sample, and multiple pathogens were present in two samples. Eighty-five (70.0%) patients provided urine samples (N_{tests} = 85, P_{Ev} = 0.70), 23 of which were positive for pneumococcal antigen (P_{Pos} = 0.27).

Cost calculations. The costs per dosage of antibiotic in our hospital ranged from €0.80 for penicillin G (€1 is equal to US$1.13) to €35.00 for ceftriaxone. Average material costs

TABLE 1. Ultimate microbiological outcomes

Microbiological cause	Total no. (%) of patients	Detection method	No. (%) of patients
S. pneumoniae	27 (22.1)[a]	Sputum culture	9 (7.4)
		Blood culture	8 (6.6)
		Urinary antigen test	23 (18.9)
Haemophilus influenzae	3 (2.5)	Sputum culture	
Staphylococcus aureus	8 (6.6)	Sputum culture	8 (6.6)
		Blood culture	2 (1.6)
Klebsiella pneumoniae	3 (2.5)	Sputum culture	
Moraxella catharralis	2 (1.6)	Sputum culture	
C. pneumoniae	12 (9.8)		
L. pneumophila	3 (2.5)	Serology	3 (2.5)
		Urinary antigen test	2 (1.6)
M. pneumoniae	2 (1.6)	Serology	2 (1.6)
Escherichia coli	5 (4.1)	Sputum culture	4 (3.3)
		Blood culture	1 (0.8)
Citrobacter freundii, *Corynebacterium*, *Streptococcus oralis*, *Enterobacter cloacae*, *P. aeruginosa*	1 (0.8)		
No microbiological cause	68 (55.4)		
Multiple pathogens	13 (10.7)		

[a] Twelve (9.8%) patients had only a positive urinary antigen test result.

(needles, syringes, infusion fluids, etc.) were €7.51 per dosage. The average time for preparation and administration of antibiotics was 4 min 25 s (range, from 4 min to 4 min 50 s) per dosage, which would mean average nurses wages of €0.89 per dosage prepared. When the number of dosages per day and preparation and handling costs were included, amoxicillin was the cheapest (€34.53 per day) and penicillin G, which was given six times daily, was the most expensive (€55.23 per day). The calculated costs of combinations of therapy per day were €91.15 for amoxicillin-clavulanic acid in combination with erythromycin and €95.82 for ceftriaxone in combination with erythromycin (Table 2).

The cost for Gram staining of sputum was €2.42 (€0.78 for material costs and €1.64 for wages for personnel). The cost for a urinary antigen test for pneumococcal pneumonia was €21.39 (€15.80 for material costs and €5.59 for wages for personnel).

Gram staining of sputum. Use of the data for our patient population and equation 1 results in the following algorithm for cost reduction: $(122 \cdot 0.19 \cdot 0.13 \cdot \Delta P) - (52 \cdot 2.42) = \ldots$

When targeted therapy consists of amoxicillin given three

TABLE 2. Antibiotic preparation and total costs for different antibiotic regimens

Antibiotic(s)	Dosage[a]	Cost (€)			
		Total preparation costs for 3 days[b]	Drug cost for 3 days	Total cost for 3 days	Cost/patient/day
Penicillin G	1 mU q 4 h	151.20	14.50	165.70	55.23
Amoxicillin	1,000 mg q 8 h	75.60	27.98	103.58	34.53
Amoxicillin-clavulanic acid	1,200 mg q 8 h	75.60	40.60	116.20	38.73
Ceftriaxone	2,000 mg q 24 h	25.20	105.00	130.20	43.40
Augmentin[c]-erythromycin	1,200 mg q 8 h/1,000 mg q 8 h	151.20	122.26	273.46	91.15
Ceftriaxone-erythromycin	2,000 mg q 24 h/1,000 mg q 8 h	100.80	186.66	287.46	95.82
Augmentin-azithromycin	1,200 mg q 8 h/500 mg q 24 h orally	75.60	57.56	133.16	44.39
Ceftriaxone-azithromycin	2,000 mg q 24 h/500 mg q 24 h orally	25.20	121.96	147.16	49.05
Average cost of antibiotics instituted				137.17	45.72

[a] q 4 h, q 8 h, and q 24 h, dosing every 4, 8, and 24 h, respectively.

[b] Preparation costs were measured by using an average preparation time plus an administration time of 4 min 25 s per dosage, which means that nurses wages were €0.89 per dosage; average material costs (needles, syringes, intravenous solutions) were €7.51 per dosage prepared. Total preparation costs per dosage are based on the average.

[c] Augmentin consists of amoxicillin and clavulanate potassium.

times daily (€103.58) and the recommended initial therapy consists of the most expensive empirical regimen (ceftriaxone and erythromycin; ΔP = €183.88), the cost reduction would be €428.26 for the total population (€3.51 per patient). However, when the cost of targeted therapy is compared to the actual average cost for the initial therapy prescribed for our population (ΔP = €33.55), the use of Gram staining would cost €24.74 (€0.20 per patient).

When the cost of targeted therapy with penicillin G given six times daily (€165.70) is compared to the cost of initial therapy with the most expensive empirical regimen (ceftriaxone and erythromycin; ΔP = €121.76), the use of Gram staining would result in a total cost savings of €241.07 (€1.98 per patient). In contrast, compared to the cheapest regimen (amoxicillin-clavulanic acid; ΔP = −€49.50), the use of Gram staining would cost €275.00 (€2.25 per patient). Compared to the average costs for the initial therapy prescribed for our patient population (ΔP = −€28.75), the use of Gram staining would cost €211.93 (€1.74 per patient).

Urinary pneumococcal antigen testing. For urinary testing, equation 1 results in the following algorithm for cost reduction: $(122 \cdot 0.70 \cdot 0.27 \cdot \Delta P) - (85 \cdot 21.39) = \ldots$

When targeted therapy consists of amoxicillin (€103.58) given three times daily and the recommended initial therapy consists of the most expensive empirical regimen (ceftriaxone and erythromycin; ΔP = €183.88), the cost reduction is €2,421.76 (€19.85 per patient). However, when the cost of targeted therapy is compared to the actual average costs for initial therapy prescribed for our population (ΔP = €33.55), the use of urinary antigen testing would cost €1,044.55 (€8.56 per patient).

When therapy with penicillin G given six times daily (€165.70) is compared to the most expensive empirical regimen (ceftriaxone and erythromycin; ΔP = €121.76), the use of urinary antigen testing would result in a cost savings of €989.39 (€8.11 per patient). In contrast, compared to the cost of the cheapest regimen (amoxicillin-clavulanic acid; ΔP = −€49.50), the use of urinary antigen testing would cost €2,959.52 (€24.26 per patient). Compared to the average costs for initial therapy (ΔP = €28.57), the use of urinary antigen testing would cost €2,476.91 (€20.30 per patient).

The cost calculations are displayed in Table 3.

Sensitivity analysis. Evidently, when P_{Pos} is high, when P_{Ev} is greater, or when ΔP is greater, the cost outcome of rapid diagnostic tests will be influenced. As is clear from the algorithm, the influence of P_{Pos}, P_{Ev}, and ΔP are of equal importance on cost outcome. A sensitivity analysis was performed by calculating the cost outcomes when these parameters were varied. The associations between ΔP, P_{Ev}, and P_{Pos} and the resulting cost per patient per day are depicted in Fig. 1. For example, when targeted therapy with amoxicillin is compared with the most expensive empirical regimen in our setting, 8.1% of the patients need to have a positive urinary antigen test result to reduce costs.

TABLE 3. Cost calculations[a]

Characteristic	Variable	Gram staining	Urinary antigen test for pneumococci
No. of patients	N_p	122	122
Proportion of evaluable samples	P_{Ev}	0.19	0.71
Proportion of positive samples	P_{Pos}	0.13	0.26
Price difference[b]	ΔP		
When pencillin G as targeted therapy was compared to:			
Ceftriaxone-erythromycin		121.76	121.76
Amoxicillin-clavulanic acid		−49.50	−49.50
Average antibiotic cost		−28.75	−28.75
When amoxicillin as targeted therapy was compared to:			
Ceftriaxone-erythromycin		183.88	183.88
Average antibiotic cost		33.55	33.55
No. of tests performed	N_{tests}	52	85
Cost for diagnostic procedure	C_{Dx}	2.42	21.39
Cost reduction[b]			
When penicillin G as targeted therapy was compared to:			
Ceftriaxone-erythromycin		1.98	8.11
Amoxicillin-clavulanic acid		−2.25	−24.26
Average antibiotic cost		1.75	−20.30
When amoxicillin as targeted therapy was compared to:			
Ceftriaxone-erythromycin		9.68	19.85
Average antibiotic cost		0.85	−8.56

[a] Cost reductions were calculated by using equation 1.
[b] Costs are in euros per patient.

DISCUSSION

We have formulated an algorithm to calculate potential cost savings when rapid diagnostic testing is used to target empirical antimicrobial therapy for CAP. The use of Gram staining and urinary antigen tests did not appear to reduce health care-associated costs in our situation. The cost reduction is influenced by price differences between targeted therapy and nontargeted therapy and the proportion of positive test results. The algorithm provides a means to determine potential cost savings in any given setting and can also be applied when new rapid diagnostic tests are evaluated.

The lack of cost reduction in our setting is explained by the small proportion of patients (19%) who were able to provide useful sputum samples, the small proportion of samples that were positive for pneumococci (Gram staining, 13%; urinary antigen testing, 27%), and the small price difference between narrow-spectrum and broad-spectrum therapy. The cost reduction would increase if more samples were evaluable and positive. The reported percentages of adequate and positive samples ranged from 24 to 39%, depending on the time interval between admission and processing of samples and supervision during collection (7).

In addition, when the cost difference between broad-spectrum and targeted therapy increases, the cost reduction also increases. In settings in which empirical therapy is more ex-

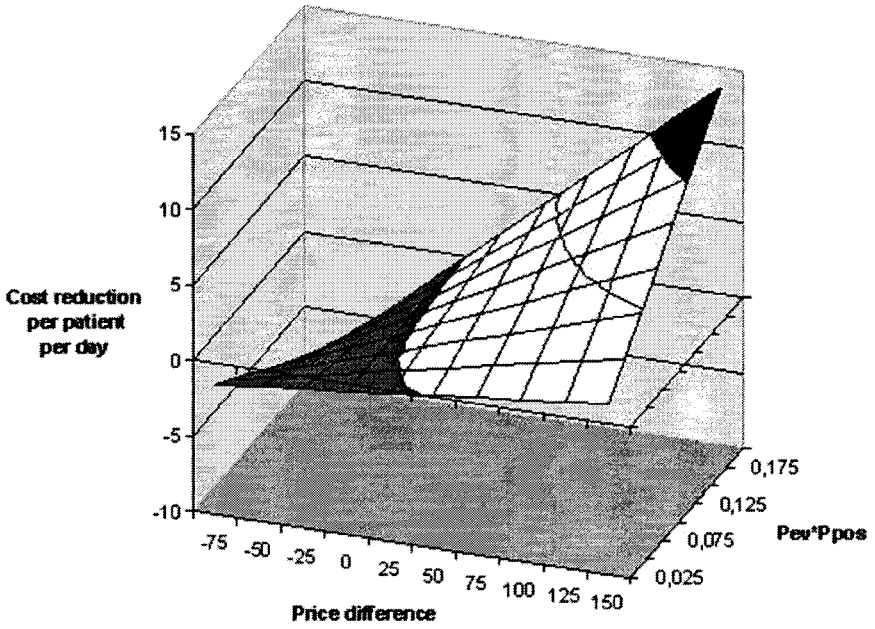

FIG. 1. Sensitivity analysis for Gram staining of sputum. The *x* axis shows the variation in the difference in price between broad-spectrum therapy and targeted therapy. Negative values mean that targeted therapy is more costly than broad-spectrum therapy. The *y* axis shows the cost reduction per patient per day. The *z* axis shows the proportion of patients with positive test results ($P_{Ev} \cdot P_{Pos}$). The values vary from 2.5 to 17.5%.

pensive, streamlining may have a greater impact on cost reduction. In our hospital, recommended empirical treatment for patients hospitalized with CAP consists of monotherapy with a β-lactam agent. Addition of a macrolide is not recommended unless the pneumonia is severe and requires patient admission to an intensive care unit or when a strong suspicion of atypical pneumonia exists (25). The cost reduction will also increase if broad-spectrum therapy is associated with extra costs, for example, additional costs due to adverse events.

Several scenarios will result in a cost reduction lower than that estimated in our study. The possibility of false-positive results (3, 19, 20)—for example, when staphylococci, although a rare cause of CAP, are falsely identified as streptococci—and the inability of Gram staining and urinary antigen tests to identify atypical infections or coinfections could result in inappropriate antimicrobial therapy and lower clinical cure rates. Furthermore, cost savings will never be achieved when test results have no impact on treatment decisions. The small impact of microbiological investigations on treatment decisions has been noted by several investigators (7, 26). Evidently, cost reductions decrease when the difference between the cost of broad-spectrum therapy and that of targeted therapy decreases, for example, as a result of the use of once-daily dosing regimens with broad-spectrum therapy instead of regimens containing penicillin G six times daily.

This study was designed to investigate the cost-benefit of streamlining initial antibiotic therapy when rapid diagnostic tests are used to detect pneumococcal pneumonia. Because of this perspective, we did not take into account other possible disadvantages of using unnecessary broad-spectrum therapy, such as antimicrobial effectiveness or the long-term effects of antibiotics on antimicrobial resistance. Whether targeted therapy is more effective than broad-spectrum therapy remains unclear. Recent analyses have suggested that initial therapy with a β-lactam and a macrolide antibiotic increases rates of survival among patients with CAP, even when pneumococci are the causative microorganisms (6, 10, 12, 18, 24, 27). From this point of view, early recognition of the causative microorganism would not be beneficial. However, these studies are retrospective and are possibly subject to prescription bias, showed inconsistencies in the reported outcomes, and provided no data on whether targeted therapy based on the results of microbiological investigations influenced patient outcomes (4, 16). In addition, unnecessary use of broad-spectrum antibacterial agents enhances the induction of antimicrobial resistance. In theory, financial investment in methods that allow rapid streamlining of antibiotic therapy may outweigh the costs associated with the future treatment of infections caused by less susceptible microorganisms.

In conclusion, we showed that the use of sputum Gram staining or the urinary antigen test to streamline initial therapy in patients hospitalized with CAP would not be associated with cost savings in our setting. However, the clinical efficacies of different antibiotics and the long-term effects on antimicrobial susceptibility were not evaluated. Moreover, differences in the costs of empirical treatment and the proportion of evaluable and positive tests may lead to different cost reductions. Our algorithm is an easy tool for calculation of such cost reductions.

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